Hematopoietic Stem Cell Transplantation for Older Patients With Myelodysplastic Syndromes

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Abstract
Myelodysplastic syndrome is primarily a disease of older age, and hematopoietic cell transplantation is the only treatment modality that offers the potential of cure and long-term survival to a substantial proportion of patients. Transplantation is used with increasing frequency in older patients, and patients in the seventh or even eighth decade of life have been transplanted successfully. However, transplant outcome strongly depends on the disease characteristics and comorbid conditions, which tend to be common in older individuals and profoundly affect nonrelapse mortality. This is a major reason why in patients older than 60 years, typically only conditioning regimens of reduced intensity are used. However, although these regimens are associated with little acute toxicity, the probability of relapse tends to be higher than with high-intensity regimens. In addition, chronic graft-versus-host disease occurs in as many as 50% to 60% of patients. Manifestations are mild in a proportion of patients; others require long-term treatment, generally with glucocorticoids, which often are not well tolerated in older individuals. Although considerable progress has been made over the past decade, more work is needed, particularly to reduce the incidence of severe graft-versus-host disease and prevent posttransplant relapse. (JNCCN 2013;11:1227–1233)

The median age of patients at diagnosis of myelodysplastic syndromes (MDS) is close to 75 years. The incidence of MDS in that age range has been estimated to be 30 to 50 cases per 100,000 a year. Although some patients will do well for a decade or longer with conservative management, others present with high-risk disease and experience rapid progression. The average survival for all patients diagnosed with MDS is approximately 3.0 to 3.5 years. The FDA-approval of several drugs for the treatment of MDS offers patients ambulatory therapy with very mild or modest side effects, and many patients in the seventh, eighth, and even ninth decades of life are being treated with hypomethylating agents or lenalidomide (and with investigational drugs). Hematologic improvements, even without achieving complete remission, have been associated with extended survival. However, the duration of responses has been in the range of 9 to 10 months with hypomethylating therapy, and 2.0 to 2.5 years for patients with del(5q) treated with lenalidomide.

The only currently available therapy that offers the potential of cure is hematopoietic cell transplantation (HCT). However, although patients in their 60s and 70s may be in better biological shape today than similar patients were a generation ago, older individuals still tend to poorly tolerate aggressive cytotoxic therapy, such as used traditionally in preparation for HCT, because of a decline in biologic reserve and the development of compromising comorbid conditions.

Over the past decade, novel transplant conditioning regimens with a low incidence of acute toxicity have been designed and administered to older patients, even in the outpatient setting. Although the proponents of this reduced-intensity conditioning (RIC), or nonmyeloablative, transplant approach have aggressively pursued HCT of older patients with MDS, other investigators have more cautiously weighed the pros and cons, with a focus on life expectancy and quality of life without HCT. No trial has yet prospectively compared the long-term outcome in older patients treated with HCT versus nontransplant management, nor have conditioning regimens of different intensity been compared.
in a controlled prospective fashion. Studies such as these are currently underway.

Who is a Candidate for Transplantation?

Until approximately 15 years ago, many transplant teams would not have transplanted patients older than 55 years. In the meantime, the upper age limit has risen quickly to 60, 65, 70 years, and even higher.10-13

Analysis of results reveals that it was not so much the chronologic age of patients that determined outcome, but rather the overall status of the patient at the time of HCT, specifically the presence of comorbid conditions, including diabetes, cardiovascular disease, pulmonary function impairment, or prior treatment for a solid tumor.14 Almost without exception, reports have shown a significant inverse correlation between the probability of transplant success (survival in remission) and comorbidities as scored by the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI).9,15 Similar conclusions have been drawn using the index described by Parimone et al,16 which is heavily focused on lung function and includes several transplant characteristics, particularly the transplant donor choice. The HCT-CI is, of course, also relevant for younger patients; however, because of the increasing frequency of comorbid conditions with increasing age, it has a particularly strong impact in older individuals. In a previous study in patients with chronic myelomonocytic leukemia, patients with an HCT-CI of less than 3 had a probability of long-term survival in remission of approximately 55% compared with 27% in patients with a score of 3 or greater.17 Similar results have been reported for patients with other diagnoses.18 Comorbidities are, in general, immutable, although hypertension can be treated and diabetes can be controlled effectively; the recent availability of JAK2 inhibitors has raised the question of whether controlling symptoms (in patients with myeloproliferative disorders) would make the patients better candidates for HCT.18 Similarly, the authors and others have shown that iron overload, associated with the MDS disease process itself or related to red blood cell transfusions, negatively impacts transplant outcome, and iron chelation might attenuate that effect.19-21 In principle, however, adjustment of the regimen to be used in preparation for HCT is the only uniformly applicable approach.

The most crucial factors when discussing transplant decisions are, of course, the disease stage and characteristics, which profoundly affect transplant outcome. Various classifications and prognostic scoring systems have been developed based on marrow myeloblast count, cytogenetics, the degree of blood cytopenias, transfusion dependence, marrow fibrosis, and patient age and performance level.22-24 The strongest risk factor driving the disease and determining posttransplant outcome is the disease karyotype.25 Patients with poor-risk cytogenetics (by IPSS [International Prognostic Scoring System] criteria), and even more so patients with very-high-risk cytogenetics according to the revised IPSS-R criteria, have a very poor outcome after HCT, primarily related to relapse, which may occur in as many as 40% of patients.26 This may be even more of an issue in older patients because of the use of RIC regimens. However, nonrelapse mortality (NRM) is also increased in these patients compared with those with lower-risk disease. Many efforts directed at reducing the post-HCT incidence of relapse have relied on intensification of the conditioning regimen. This, however, has proven counterproductive, even in young patients, because any gain in reducing the relapse incidence was accompanied by increased NRM and, ultimately, similar outcomes.27

Nontransplant Therapy and Its Impact on HCT

Considerable effort has gone into determining whether pretransplant therapy (debunking, reduction of tumor burden) would improve posttransplant outcome. However, no data from controlled prospective trials are available. One initial concern was that pre-HCT therapy would negatively impact post-HCT toxicity and NRM, particularly in older patients previously exposed to high-dose chemotherapy. Available data suggest that this is not a major issue; in fact, a well-designed strategy of chemotherapy followed by a conditioning regimen that takes into consideration the intensity of pre-HCT treatment would gradually separate the side effects of debunking (an intended goal of conventional conditioning) from the cytokine storm and its effects related to allogeneic HCT. The use of hypomethylating agents such as 5azacitidine or 5-aza-2’-deoxycytidine, instead of induction-type chemotherapy, has led to even bet-
ter tolerability, although whether these modalities have comparable efficacy remains to be determined in a controlled trial.\textsuperscript{28–32} However, if hypomethylating therapy does not result in the reduction of the proportion of myeloblasts, patients often are given induction chemotherapy, with reported mortality rates of 10\% to 15\%, primarily in older patients.\textsuperscript{33} According to clinical wisdom, reducing the tumor burden as measured by the proportion of marrow myeloblasts will enhance the probability of relapse-free survival (RFS) after HCT. No data suggest that a similar approach will improve the chances of success in patients presenting with high-risk cytogenetics, and a significant proportion of patients may not make it to transplantation because of the morbidity and mortality of the intensified induction approach.

Retrospective analyses have shown similar survival/mortality for patients given hypomethylating therapy and those undergoing HCT, at least for the first 2 years.\textsuperscript{34} With further follow-up, the survival curves diverge in favor of HCT. In principle, this pattern was confirmed recently in a decision analysis, which showed that older patients with low-risk MDS (IPSS risk categories low and intermediate 1) were unlikely to derive benefit from HCT, whereas those with high-risk disease (IPSS risk categories intermediate 2 and high) could expect a benefit (increased life expectancy), albeit only with considerable delay after HCT.\textsuperscript{35} These reports raise important questions as to how clinicians should advise older patients. A registration trial is currently underway that will follow patients with MDS and attempt to determine prospectively advantages or disadvantages of HCT in older patients with MDS.

**Timing of Transplantation**

Analysis of transplant data has shown consistently that patients with low-risk MDS and those transplanted early in their disease course have a higher probability of long-term survival in remission than patients transplanted at a more advanced stage of MDS. This pattern is, presumably, related to the fact that the hematopoietic clones underlying MDS become more resistant as the disease progresses, possibly because of upregulation of CD47 and TWIST1 and evasion of apoptosis.\textsuperscript{36,37} New or previously covert clones with new cytogenetic and molecular defects may also emerge.\textsuperscript{38} In addition, patients may acquire new comorbidities over the disease course, thereby adding to the risk of NRM. However, these patients may also benefit from nontransplant approaches (see earlier discussion). The definition of low risk is also important. For example, a younger patient who is red cell transfusion–dependent might be considered for HCT sooner, despite being categorized as having low-risk MDS.\textsuperscript{39}

Of course, patients who are doing well on little or no therapy are unlikely to require HCT, and therefore this is generally performed only at a more advance stage. With the availability of hypomethylating agents, the decision regarding whether to perform HCT has become even more of a challenge. Patients whose disease is responding to hypomethylating therapy typically elect to continue treatment with those agents, and do not undergo transplantation. This approach seems to be more frequent in older than in younger patients. However, evidence also suggests that the probability of long-term success decreases steeply in patients who undergo HCT after disease progression occurs while on hypomethylating therapy.\textsuperscript{40} In fact, one retrospective analysis found that although the median survival was prolonged in patients after transplant, the median life expectancy was only approximately 14 months and no plateau was reached.\textsuperscript{40} Results were substantially superior, with approximately 35\% of patients surviving long term, if transplants were performed before any disease progression was observed. This observation raises numerous issues regarding the importance of quality of life, which may be good without HCT; life expectancy may be extended with HCT, but quality of life may be affected by the potential sequelae of HCT.\textsuperscript{41,42} Although many patients with MDS who have undergone successful transplants have been followed now for more than 2 decades, the question of whether to perform HCT at the time of best response to therapy (nontransplant) versus at disease progression remains controversial.

**What is the Optimum Transplant Approach?**

Most transplant centers will try to identify an HLA-matched sibling donor as a first approach. If no HLA-identical sibling is available, generally a search is initiated for an unrelated donor, matched through high-resolution HLA typing. Because sibling donors
are typically close in age to the patient, the older the patient, the more likely that the prospective donor has (age-related) medical conditions. Occasionally these donors will be diagnosed during the pretransplant workup as having, for example, a malignancy or cardiovascular disease, and therefore may not qualify as donors. In addition, the question has been raised recently whether transplants from fully HLA-matched but younger unrelated donors might be associated with better transplant outcomes than observed with HLA-matched yet older related donors. However, a recent analysis of outcome in more than 2000 patients (related donors ≥50 years, unrelated donors <50 years) showed superior survival with related donors in patients with good performance status, and comparable outcome with related and unrelated donors in patients with poor performance scores.

Additional options include the use of umbilical cord blood or HLA haploidentical related donors. The authors believe that including these 2 sources of stem cells will allow transplantation to be offered to almost every patient, and only the patient’s condition and disease stage will be limiting factors. Nevertheless, the focus has remained on HLA-matched donors, and results with related and unrelated donors in general have been comparable, although a somewhat higher incidence of graft-versus-host disease (GVHD) is seen with unrelated donors, perhaps in the range of 50% to 60% for the acute and chronic forms. The experience with HLA-haploidentical donors or unrelated cord blood is significantly more limited in MDS than in other diagnoses. Delayed immune recovery and slow engraftment are major concerns. In general, transplantation from these alternative donors is associated with increased NRM.

With a donor identified, what is the optimum transplant approach for the older patient? To adhere to the Socratic oath, “primum nil nocere,” the transplant approach should carry a minimal risk of toxicity and mortality, allowing as many patients as possible to reach the point where they can reap the benefit of HCT—survival in remission—without clinically significant GVHD and organ dysfunction.

Intensive efforts have been directed at “nontoxic” conditioning regimens. Although the literature often contrasts “nonmyeloablative” with “myeloablative” regimens, a continuum of different intensity regimens is currently in use, all aiming at minimum toxicity and maximum efficacy. However, for patients aged 60 or 65 years and older, transplant centers generally have used RIC regimens that combine, for example, fludarabine and melphalan, or fludarabine and total body irradiation at doses of 2 to 4 Gy. Others have reduced the classic busulfan dose of 16 mg/kg (over 4 days) to 8 mg/kg over 2 or 4 days in combination with fludarabine at doses between 30 and 50 mg/m² for 3 to 5 days. Summarizing results obtained at 3 centers, Laport et al reported on 148 patients with MDS or MDS/myeloproliferative neoplasms. The median age of the patients was 59 years. With a median follow-up of 4 years, the 3-year RFS was 27% for all patients, approximately 40% for good-risk patients, and maybe only 15% for high-risk patients. The 3-year incidence of relapse was 41%, and NRM was 32%. As in numerous other studies, patients who developed chronic GVHD had a lower incidence of relapse than did those without GVHD. One issue in patients with MDS, who are generally not pretreated with intensive chemotherapy, has been graft failure when RIC regimens were used; in the report by Laport et al, the incidence was approximately 15%. Importantly, however, no data from prospective, controlled studies are available, and the selection of patients for HCT in the retrospective analyses clearly was subject to selection bias: patients with high comorbidity scores and, hence, at risk for NRM, were not offered HCT.

Retrospective analyses that have compared outcome with high-intensity conditioning (myeloablative) versus outcome with RIC (nonmyeloablative) regimens have consistently shown comparable results in highly selected patients: although the cumulative incidence of NRM tends to be lower with low-intensity regimens, the relapse incidence is higher. As a result, no net gain in RFS is obtained compared with high-intensity regimens (showing lower relapse rates, but higher NRM). Furthermore, many of the reported studies included younger patients who received RIC because of comorbidities rather than on the basis of age. Therefore, the decision regarding HCT, such as in a patient aged 65 years or older, must be based entirely on the comorbid conditions and biological age (as ill-defined as that may be) and the patient’s commitment to HCT. Some centers have defined the upper age limit for transplantation as 75 years.
The Posttransplant Course

A major challenge after HCT transplantation is disease relapse. This problem is currently being approached by modifying conditioning regimens, but also by preemptive or therapeutic treatment, for example with post-HCT administration of hypomethylating agents or cell-mediated immunotherapy. Because older patients are typically conditioned with RIC regimens wherein relapse is more of an issue, post-HCT interventions may be particularly relevant in older patients. A second important problem is the development of GVHD, particularly in its chronic form. Currently, all patients receiving transplants from allogeneic donors (be it related or unrelated) will receive GVHD prophylaxis with a calcineurin inhibitor such as cyclosporine or tacrolimus, in combination with mycophenolate mofetil or methotrexate, and, in some studies, sirolimus. Still, approximately 50% of patients will develop an acute form of GVHD, and a similar proportion will develop chronic GVHD (acute GVHD being the major risk factor for chronic GVHD). Patients who do develop chronic GVHD on average will require treatment for approximately 2.5 years. Older patients tend to do less well than younger individuals, at least partially related to the fact that first-line treatment of GVHD is still with glucocorticoids, which often are poorly tolerated by older patients. Treatment-associated metabolic changes, particularly hyperglycemia, may be difficult to manage and may further aggravate the risk of infections. Furthermore, myopathy may lead to reduced activity, associated reduced respiratory effort, retention of secretion, and further enhancement of infections. Effects on bone mass are somewhat more delayed but can be severe in older patients.

Summary

The development of novel conditioning regimens has made transplantation available to an increasing number of patients, and patients up to 80 years of age have undergone successful transplantation. However, the decision to perform or not perform HCT remains difficult. A recent analysis of RIC regimens in older patients has shown that patients with IPSS low- or intermediate-1–risk MDS typically do not benefit from HCT. Patients with IPSS intermediate-2 or high risk stand a good chance of benefiting; however, the benefits may become prominent only after a follow-up of several years. Therefore, patients must understand the commitment they make when going to transplantation and what risks they are facing. Some transplant physicians will argue that the worst that can happen is that the disease will recur and patients may be back at the point they were before HCT. However, relapse may occur even in the presence of chronic GVHD, and the patient may then be left with both recurrent disease and GVHD, frequently associated with a significant symptom burden. The presence of GVHD is generally considered a contraindication for the infusion of donor lymphocytes, one of the modalities used to treat post-HCT relapse. Ongoing studies suggest that posttransplant administration of hypomethylating agents may be beneficial both for preventing relapse and for attenuating GVHD, although no controlled studies are currently available.

References

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